

REMARKS

Claims 1-15 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the prior Office Action.

Claim Amendments

The preamble of claim 1 has been amended to further clarify the present invention, which recognizes and solves the problem of intra-support variability in the synthesis of nucleic acid arrays. Accordingly, Claim 1 has been amended to recite “[a] method of reducing intra-support variability in a nucleic acid array synthesized on a support, wherein the support has a surface upon which said nucleic acid array is synthesized, wherein each nucleic acid occupies a separate localized area of the support...” Support for this amendment can be found in numerous places in the specification, for example, on page 2, lines 23-33. No new matter has been added.

1. Corrections to the Record

In the Final Office Action dated February 16, 2005, the Examiner states that “the previous rejections in the Office Action dated 4 [sic] September 2004 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments.” Applicants respectfully point out that the Office Action mailed September 2, 2004 made *no rejections* under 35 U.S.C. 112, second paragraph. Furthermore, Applicants’ Reply to the September 2, 2004 Office Action, mailed December 2, 2004, made *no amendments*. Clarification is respectfully requested.

2-3. Rejection of Claims 1-15 Under 35 U.S.C. 103(a) Over Winkler et al. in View of Goldberg et al.

Claims 1-15 stand rejected as allegedly obvious over US 5,885,837 to Winkler et al. (“Winkler”) and US 5,959,098 to Goldberg et al. (“Goldberg”). The Examiner previously acknowledged that Winkler does not teach a vertical substrate position (it is assumed that the statements regarding Winkler and vertical positioning on page 3, lines 9-15 are vestigial, in view of Applicants’ prior remarks and the Examiner’s withdrawal of the rejection under 35 U.S.C. 102(b)). The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the vertical positioning of Goldberg to the

synthesis of Winkler “for the expected benefit of facilitating bubble removal as taught by Goldberg et al.” Applicants respectfully traverse the rejection.

Applicants respectfully maintain that there is no motivation or suggestion for one of ordinary skill in the art to combine the method of Winkler with the vertical flow cell positioning of Goldberg. The Examiner states “*Goldberg* specifically teaches the bubble formation problem and [*Goldberg* teaches] the problem’s solution...hence, one of ordinary skill in the art of array production would have been motivated to avoid bubble formation problems based on the teaching of *Goldberg*” (emphasis added). However, there is no evidence linking the problem of *Goldberg*, that of bubble formation, to the method of Winkler. According to MPEP 2143.01, in order to combine references there must be “some teaching, suggestion, or motivation to do so found either . . . in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” Without evidence that bubble formation is a problem in Winkler, it is improper to combine Winkler with Goldberg. Accordingly, Applicants maintain their position from the Reply of December 2, 2004, that there is no hint or suggestion in Winkler that bubble formation is even a consideration, much less a problem, and, as such, there is no motivation to combine the teachings of Winkler and Goldberg.

Furthermore, the instant claims, as currently amended, are directed to a method for “reducing intra-support variability in a nucleic acid array synthesized on a support.” Neither Winkler nor Goldberg either alone or in combination disclose such a method. In particular, there is no evidence in the art of record that the problem of intra-support variability in the synthesis of vertically held arrays was known prior to the time of the present invention. There is no evidence that Winkler or Goldberg were aware of the problem or the benefits of the instant method. Case law holds that the inventive concept to be tested under the obviousness standard may include discovery of a problem as well as the solution to a problem. For example, in *Eibel Co. v. Paper Co.* (261 U.S. 45, 68 (USSC 1923)), the court stated:

The invention was not the mere use of a high or substantial pitch to remedy a known source of trouble. It was the discovery of the source not before known, and the application of the remedy, for which Eibel was entitled to be rewarded in his patent.

Furthermore, the discovery of the source of a recognized problem can be part of the “subject matter as a whole [sought to be patented].” *In re Sponnoble*, 405 F.2d 578, 160 USPQ 237

(CCPA 1969). In the instant application, not only have Applicants remedied a problem, that of intra-support variability, but Applicants have also identified the problem by discovering that when the substrate is held in a substantially vertical position during array synthesis, there can be large intra-support variation in the product (see, for example, page 2, lines 23-33). As noted in *Eibel*, the discovery of the source of a problem has long been evidence for the non-obviousness of the solution. Accordingly, Applicants assert that the instant claims are not obvious in view of the cited art. Applicants respectfully request reconsideration and withdrawal of the rejection.

4. *Rejection of Claims 1-15 Under 35 U.S.C. 103(a) Over Gamble et al. in View of Winkler et al.*

Claims 1-15 stand rejected as allegedly obvious over US 5,981,733 to Gamble *et al.* (“Gamble”) in view of Winkler. Applicants traverse the rejection to the extent that it is maintained over the claims as currently amended.

As noted above, the instant claims have been amended to recite a method for “reducing intra-support variability in a nucleic acid array synthesized on a support.” Neither Winkler nor Gamble either alone or in combination disclose such a method. Indeed, the problem of intra-support variability was not recognized by either Winkler or Gamble. Instead, Applicants were the first to discover this problem and then devised a solution, as claimed in the present application. As discussed above, discovery of a problem and its solution are evidence of non-obviousness.

Although it is believed that the claims, as amended, are clearly non-obvious in view of the cited references, Applicants wish to address the remarks made in the present Office Action. The Examiner states that Applicants’ prior arguments are unpersuasive because “Winkler specifically teaches that different flow patterns are desired in the methods of array production.” Applicants disagree and maintain their arguments of record, namely that Gamble teaches a method in which the *entire* surface of the substrate is coated with reagent in each attaching step, a method that is antithetical to that of Winkler, in which reagents are *selectively* delivered to channels. Contrary to the Examiner’s assertions, specific channel surfaces on the surface of a substrate are not equivalent to nor interchangeable with the entire surface of the substrate, especially in methods employing complex machines that are designed to perform the exact

movements required to deliver reagents to channels or to entire surfaces during the syntheses of arrays.

Moreover, the Examiner contends that Winkler and Gamble share “the same principle of operation i.e. array synthesis by flowing reagents over a surface.” Again, this is an overly broad analysis of the principle of operation of the devices in Winkler and Gamble. At the very least, the principles of operation of the Winkler and Gamble devices must account for the manner in which the arrays are prepared, those methods being the use of discrete channels for reagent delivery and the non-selective coating of an entire substrate surface. Clearly, a selective channel method and a global substrate surface coating method are not equivalent, interchangeable, nor compatible. As such, Applicants maintain their previous arguments that there is no motivation to modify the machine of Winkler with attributes from the machine of Gamble, particularly because they do not share the same principle of operation.

In summary, Applicants have discovered and solved the problem of intra-support variation in nucleic acid arrays, and the claims have been amended to clarify this point. Although Gamble and Winkler cannot properly be combined, the combined teachings of the cited references nonetheless do not teach or otherwise suggest the present invention. Thus, the pending claims are not obvious over Winkler in combination with Gamble. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7725. Should an extension of time be required, Applicants hereby petition for same

and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Dated: May 17, 2005

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